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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,399	11/23/2001	George Jackowski	2132.091	4956

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EXAMINER	
CHERNYSHEV, OLGA N	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/993,399	JACKOWSKI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 39-46* is/are pending in the application.

4a) Of the above claim(s) *39-43,45 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *two pages GE catalog printout*.

DETAILED ACTION

Response to Amendment

1. Claims 1, 39 and 44-46 have been amended as requested in the amendment filed on December 14, 2006. Following the amendment, claims 1 and 39-46 are pending in the instant application.

Claims 39-43 and 45-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed on July 28, 2005.

2. Claims 1 and 44 (in part) are under examination in the instant office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed on April 11, 2006 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1 and 44 stand rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility essentially for reasons of record in Paper mailed on December 20, 2005.

Claims 1 and 44, as currently presented, are directed to a biopolymer marker consisting of SEQ ID NO: 1, which evidences a link to Alzheimer's disease (AD). The instant specification provides a disclosure of a protocol, under which samples of blood collected from AD patients, age-matched controls and pooled control samples were analyzed by using chromatographic and mass spectrometric techniques. The results of the analysis are presented in Figures 1-2 and also within the text of the instant specification. Specifically, finding of the "disease specific marker" identified by an amino acid sequence is presented at page 46 of the instant specification. At page 46, Figure 1 is described as "photographs of a gel which is indicative of the presence/absence of the marker in disease vs. control and, in cases where the marker is always present, the relative strength, e.g. the up or down regulation of the marker relative to categorization of diseases state is deduced". Brief description of the figures (page 37) does not contain any disclosure of how a peptide of SEQ ID NO: 1 corresponds to the bands shown in Figure 1. The Examiner maintains that based on the information presented in the instant specification as originally filed, the instant claimed invention, an isolated biopolymer marker SEQ ID NO: 1, asserted to be useful for diagnosis and treatment of Alzheimer's disease, clearly lacks specific and substantial credible real-world utility and, therefore, the instant invention does not meet the requirements of 35 U.S.C. 101.

At p. 24 of the Response, Applicant states that "[T]he claimed biopolymer marker (SEQ ID NO: 1) is useful for diagnosis and treatment of Alzheimer's disease since it was found to evidence a link to Alzheimer's disease (an "asserted" utility). This asserted utility is supported by data, the gel shown in Figure 1, derived from the working examples which shows that the claimed peptide (SEQ ID NO: 1) is differentially expressed between Alzheimer's disease

patients and patients age matched with the Alzheimer's disease patients". Applicant further refers to appropriate sections of MPEP related to the utility requirement under 35 U.S.C. 101 (p. 24, 29 and 31). At p. 37 of the Response, Applicant submits that the Examiner's position reveals "an incomplete understanding of the invention". Applicant's arguments have been fully considered but are not persuasive for the following reasons.

Claim 1, as currently amended, is directed to a biopolymer marker consisting of SEQ ID NO: 1 which evidences a link to Alzheimer's disease. SEQ ID NO: 1 is a short, fifteen amino acid long peptide (see Sequence Listing of 03/12/2002), which is a fragment of a longer full-length naturally occurring protein molecule. According to the instant disclosure, the instant claimed biomarker was isolated from samples of blood collected from normal control individuals and was not found in AD patients. The protocol, (p. 40-46 of the specification), of the isolation is as follows: (1) protein fractions of the samples of blood are subjected to electrophoresis; (2) the bands, which are of different density are visually identified, (3) the protein content of a band that is "darker" on the gel (Fig. 1) is extracted, proteolytically cleaved by a non-specific proteinase trypsin and (4) subjected to further analysis by electrophoresis or means of mass spectrometry to identify the precise structure of the protein fragment contained within the sample. The instant specification specifically states that "[I]n the instantly disclosed invention, we deal with proteins having a molecular weight of about 20 kD or. In general, proteins of greater than 20 kD can reliably be fragmented by trypsin or other enzymes. [...] Proteins differ from peptides in that they cannot be effectively resolved by time flight MS and they are too large (>3kD) to be effectively fragmented by collision with gases. [...] Once the proteins have been resolved and visualized with stains the proteins that differ between disease states can then be excised from the

gel and the protein purified in the 1-D gel band or 2-D gel spot can be cleaved into fragments less that 3kD by proteolytic enzymes" (pp. 36-37). The same protocol is repeated and explained again at p. 37-38 of Applicant's Response.

The gel electrophoresis technique is one of the old staple tools in molecular biology, which allows identification of molecules by the band pattern according to their molecular weight. It is clear that the bands presented in Figure 1 cannot possibly represent a peptide of SEQ ID NO: 1 itself, which is only fifteen amino acids long and, therefore, cannot be seen within a gel where "high molecular weight standards" (see the box) were used to identify molecules with molecular weight between 10 and 250 kD (for the standard molecular weight markers description see also a copy of the description of the commercially available high-Range markers attached to the instant office action). By Applicant's own admission, the proteins within the gel are "greater than 20 kD" (see above and pp. 36-37 of the Response), and, as such, cannot be of SEQ ID NO: 1, which is a short fragment of 15 amino acids, clearly less than 20 kD.

The bands as seen in Figure 1 represent differential expression of a mixture of proteins of the same molecular weight (see also description provided in boxes "Band 1B" and "Band 4", which specifically recite "Unknown protein"). The protein content of bands that looked differently, was trypsinized into fragments, according to the protocol of the instant specification, and one the fragments was identified as a peptide of SEQ ID NO: 1.

Thus, it is obvious that "differential expression" of bands between AD samples and control samples as seen in Figure 1 has only relative significance with respect to the differential distribution of the instant claimed protein itself. As fully explained earlier, the Examiner does not dispute the results presented in Figure 1 or disclosed in the instant specification, as it is obvious

that the bands in columns related to AD and controls do look differently. However, this visually "observed expression pattern", followed by identification of the structure of a protein fragment within the darker looking band does not allow the immediate conclusion of finding a biomarker for AD. As fully explained in the earlier communications, the finding of a fragment of a naturally occurring human protein in a sample obtained from a normal subject and not finding that naturally occurring precursor protein in limited amount of samples of patients suspected of having AD is not sufficient to establish the specific and substantial credible utility for the instant protein fragment. One readily appreciates that many proteins are differentially expressed between healthy and "diseased" tissues; however, not all of these proteins constitute biomarkers, as molecules that allow distinguishing disease *vs*. healthy state.

It is obvious that finding a difference, any difference, between normal and pathological conditions (samples in the instant case) is the first step in hope of identifying potential markers for that pathological condition. However, one would reasonably expect that many proteins are differentially expressed during course of disease; however, not all of them can serve as diagnostic tools. The instant specification identified a peptide that is "linked" to AD by virtue of it being found in a sample of mixture of proteins artificially cleaved by proteases, such protein obtained from a normal healthy individual. However, there appears no further characterization presented that would lead to the "real world" specific utility of this peptide as biomarker for AD. There appears to be no information presented in the instant specification as to what constitutes finding of a peptide of SEQ ID NO: 1 as "evidence of a link to Alzheimer's disease".

Regarding the merit of the argument, it appears that Applicant uses phrases "evidence of a link to Alzheimer's disease" (claim 1 and throughout the text of the Response) and "a marker

for Alzheimer's disease" interchangeably. However, establishing if the instant claimed molecule represents a marker for a disease or evidences a non-specified link to a disease constitutes a major issue with respect to determination of a specific and substantial credible utility. While identification of a molecule that could serve as a diagnostic tool for clinical purposes represents an invention with a specific and substantial credible utility, the disclosure of a molecule that is described as "evidence of a link to" a disease condition is suitable only to benefit further research.

There is no argument that finding of the peptide of SEQ ID NO: 1 in protein samples artificially cleaved with non-specific proteases of normal healthy individuals when compared to samples of patients suspected of having Alzheimer's disease represents an interesting observation, which after further research and development could potentially lead to identification of the claimed peptide as a marker useful for diagnosis, or as a molecule that is useful as an indicator of a specific link shown to be associated with stage, progression or risk factor of AD, for example. However, until this further characterization is complete and practical significance of the peptide of SEQ ID NO: 1 is disclosed, the instant claimed protein fragment could only be used as an object of further research.

The instant specification asserts the use of the claimed peptide of SEQ ID NO: 1 as a diagnostic marker for AD. However, there appears to be no further information presented in the instant specification as to what constitutes finding of a peptide of SEQ ID NO: 1 in a sample. For example, if a peptide of SEQ ID NO: 1 was found in a sample obtained from a patient, what would that mean to the skilled practitioner? Does it mean that a patient does not have AD, but is at risk of developing the disease? The instant specification fails to provide any factual evidence

that finding of a peptide of SEQ ID NO: 1 could lead to any meaningful determination for diagnosis of Alzheimer's disease or would be useful for treatment of Alzheimer's diseases, as asserted by Applicant. There is less explanation presented with respect to the use of the claimed peptide for clinical purposes of treatment of AD, as also asserted by the instant specification. Thus, in order to practice the claimed invention, a skilled artisan would have to engage in a substantial amount of further research to establish the utility of the claimed peptide of SEQ ID NO: 1 in the diagnosis or treatment of Alzheimer's.

The Declaration of Ferris Lander under 37 CFR 1.132 filed on April 11, 2006 is insufficient to overcome the rejection of claims 1 and 44 based upon 101/112 as set forth in the last Office action because: The Declaration reiterates Figure 1 and presents additional explanation of the Figure description, such as "the gel provides evidence that the claimed peptide (SEQ ID NO: 1) is differentially expressed between Alzheimer's disease and age matched controls" (p. 2 of the Declaration). However, as fully explained in the previous communications of record and also earlier in the instant office action, the bands as presented in Figure 1 are either of different proteins, which are heavier/longer than fifteen amino acids, or the Figure provides the wrong high molecular weight standards and the Declaration fails to provide explanation to these discrepancies. To clarify once again the Examiner's position, there is no dispute that the bands in Fig. 1 look differently between normal and AD samples, and also it is clear that the protein mixture obtained from "normal" band, after it is enzymatically cleaved into small fragments does contain peptide of SEQ ID NO: 1, as evidenced by Figure 2; however, this, alone does not make a peptide of SEQ ID NO: 1 diagnostic of AD or suitable for treatment of AD. The instant specification, as filed does not disclose how to use the peptide of SEQ ID NO: 1 for

diagnostic or therapeutic purposes and, therefore, a skilled practitioner would have to resort to substantial amount of further research and experimentation to study and discover if the claimed peptide of SEQ ID NO: 1 has the asserted practical utility, as currently claimed.

The U.S. Court of Appeals for the Federal Circuit recently addressed the utility requirement in the context of a claim to DNA. *See In re Fisher,* 2005 WL 2139421 (Sept. 7, 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), as rejecting a "de minimis view of utility" 2005 WL 2139421, at *4. The *Fisher* court held that § 101 requires a utility that is both substantial and specific. *Id.* at *5. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Id.*

Just as in *Fisher* case where the Board reasoned that use of the claimed ESTs for the identification of polymorphisms is not a specific and substantial utility because "[w]ithout knowing any further information in regard to the gene represented by an EST, as here, detection of the presence or absence of a polymorphism provides the barest information in regard to genetic heritage," (*Id.,* slip op. at 15), in the instant case, detection of peptide of SEQ ID NO: 1 in a sample of a patient suspected of having AD provides no meaningful information as to the diagnosis determination. While an assay that detects the presence of a marker that has a stated correlation to a specific disease condition would be considered a "substantial utility" in the context of providing a diagnostic tool, in the instant case the claimed peptide is suitable only for further research, which constitutes a utility that is not considered a "substantial utility". See

Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court expressed the opinion that all chemical compounds are "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility.

Finally, with respect to limitation present in claim 1, "evidences a link to Alzheimer's disease", the Examiner maintains that disclosure of a peptide of SEQ ID NO: 1 as being linked to a pathological condition constitutes a utility, which requires further research to identify or reasonably confirm a "real world" context of use. At present, it appears that the only information obtained from identifying the presence of a biopolymer marker of SEQ ID NO: 1 is the determination of "a link to AD". One skilled in the art readily appreciates that many factors have a link to or are associated with a particular pathological condition. In *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), the court specifically stated that "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion". To grant Applicant a patent encompassing isolated fragments of a naturally occurring human protein, which are not readily usable in their current form, would be to grant Applicant a monopoly "the metes and bounds" of which "are not capable of precise delineation". That monopoly "may engross a vast, unknown, and perhaps unknowable area" and "confer power to block off whole areas of scientific development, without compensating benefit to the public" *Brenner v. Manson*, *Ibid*). To grant Applicant a patent on the claimed peptides based solely upon an assertion that the protein is linked to Alzheimer's disease is clearly prohibited by this judicial precedent since the compensation to the public is not commensurate with the monopoly granted.

Thus, since the instant specification does not disclose a credible "real world" use for the isolated biopolymer markers of SEQ ID NO: 1 in currently available form, then the claimed

invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1 and 44 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

9. No claim is allowed.

10. This application contains claims 39-43 and 45-46 drawn to an invention nonelected with traverse in Paper filed on July 28, 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

11. Applicant is advised that claim 44 currently comprises non-elected subject matter ("an antibody that binds to said protein"). Applicant is advised that in case of forwarding this application to the Board of Appeals, claim 44 must be amended to be limited to the subject matter, which was examined and rejected.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1649

February 27, 2007

GE Healthcare

Rainbow™ Molecular Weight Markers

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- Protein standards marked with a variety of strongly colored dyes permit visualization of the markers without supplementary staining both in the gel and on Weste membranes following protein transfer.
- Full-Range Rainbow™ Molecular Weight Markers, supplied in gel loading buffer, utilize recombinant proteins to give sharper bands of defined molecular weight (250 000).
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Product	Pack size	Product Code	List Price
Full-Range Rainbow Molecular Weight Markers	500 µl	RPN800	country select
High-Range Rainbow Molecular Weight Markers	250 µl	RPN756	country select
Low-Range Rainbow Molecular Weight Markers	250 µl	RPN755	country select

Store at -15 to -30 °C.

You may also need:				
ECL Western Blotting Detection Reagents	For 4000 cm^2 membrane	RPN2106	country select
ECL Plus Western Blotting Detection Reagents	For 1000 cm^2 membrane	RPN2132	country select
RABBIT IGG HRP LINKED WHOLE AB	1 ML	NA934-1ML	country select
ECL Western Blotting Detection Reagents	For 2000 cm^2 membrane	RPN2209	country select
ECL DualVue Western Blotting Markers	1 pack (25 loadings)	RPN810	country select
EPS 601 Power Supply	1	18-1130-02	country select

Rainbow™ Molecular Weight Markers

Technical Information

TECHNICAL SPECIFICATIONS				
Protein	M_r	Source	Reference*	Amount (µg), approx.
Full-Range Rainbow™ Molecular Weight Markers				
Recombinant protein	250 000			75
Recombinant protein	160 000			75
Recombinant protein	105 000			75
Recombinant protein	75 000			75
Recombinant protein	50 000			75
Recombinant protein	35 000			75
Recombinant protein	30 000			75
Recombinant protein	25 000			75
Recombinant protein	15 000			75

Recombinant protein	10 000			75
Low-Range Rainbow™ Molecular Weight Markers				
Ovalbumin	45 000	chicken egg white	8	250
Carbonic anhydrase	30 000	bovine erythrocyte	9	250
Trypsin inhibitor	20 100	soybean	10	250
Lysozyme	14 300	chicken egg white	16	250
Aprotinin	6500	bovine lung	18	250
Insulin chain B	3500	bovine pancreas	17	250
Insulin chain A	2500	bovine pancreas	17	250
High-Range Rainbow™ Molecular Weight Markers				
Myosin	220 000	rabbit muscle	1	250
Phosphorylase b	97 000	rabbit muscle	6	250
Albumin	66 000	bovine serum	7	250
Ovalbumin	45 000	chicken egg white	8	250
Carbonic anhydrase	30 000	bovine erythrocyte	9	250
Trypsin inhibitor	20 100	soybean	10	250
Lysozyme	14 300	chicken egg white	16	250

The ladder of proteins in the Full-Range Rainbow™ Molecular Weight Markers on a 12% SDS-PAGE gel.

Consult the technical support section for contact information

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